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## **Biologics for paediatric severe asthma: Trick or TREAT?**

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While most asthma in UK children can be controlled with low-moderate dose inhaled corticosteroids, there remains a small group with severe disease and poor control despite maximal treatment whose needs are unmet; there are stark differences in their healthcare provision compared to adults. Unlike adults, children with severe asthma are not treated at specialist centres, clinical trials of novel therapeutics are not tailored for children, and novel biologics are being approved without evidence of efficacy. In adults, severe asthma is a commissioned service with only named specialist centres able to assess patients and prescribe biologics. A systematic assessment at a dedicated severe asthma centre is associated with improved quality of life and asthma control and a reduction in health-care utilisation(1). This multidisciplinary assessment helps to identify remediable factors such as poor adherence and ensures that appropriate patients are started on costly biologics. In contrast, despite international guideline recommendations(2), there is no such service provision or specification for children in the UK and most other parts of the world, even though evidence confirms children with severe asthma have long-term morbidity, including development of chronic obstructive pulmonary disease in adulthood(3). Without specialist services children may be exposed to potential harm associated with inappropriate prescription of biologics, or be denied an appropriate therapy, while absence of accurate monitoring will result in a missed opportunity to assess the benefit of biologics across the lifespan as disease modifying agents(4).

Children with severe, therapy resistant asthma (STRA) and refractory difficult asthma(5) should be considered for biologics(2), but until July 2018, the only biologic licenced for children was the anti-IgE monoclonal antibody, omalizumab. However, the restricted prescribing guidelines, including a narrow serum IgE range, and the variable clinical response in STRA(6), has left a substantial proportion of children with unmet therapeutic needs. The exciting pipeline of biologics could help to address the needs of a wider group of children with STRA. However, we have three key concerns; firstly, that the appropriate studies are not being carried out in children (e.g. inappropriate end-points such as FEV<sub>1</sub> are selected); secondly, that drug development is aimed at therapeutic targets from adult models of disease; and thirdly, there are very little data to guide choosing the optimal biologic for individual patients.

Mepolizumab (monoclonal antibody to IL-5) dramatically reduces asthma attacks in adults. Although adolescents (>12 years) were eligible for the trials, the actual numbers included were tiny (about 30 of the total 800 plus participants). However, mepolizumab was licensed for use in children aged 6-17 years by the European Medicines Agency (EMA) in August 2018, despite the very limited efficacy data in children aged >12 years, and the complete absence of efficacy data in those aged 6-11 years. This is clearly of huge concern and contravenes European Paediatric regulations (<https://www.ema.europa.eu/en/human-regulatory/overview/paediatric-medicines/paediatric-regulation>). In contrast, omalizumab was only licenced after efficacy was shown in children aged 6-16

years(6). Although most children with STRA have steroid resistant airway eosinophilia(7,8) which should respond to mepolizumab, the eosinophilia may not be due to Thelper2 cytokines, which have been difficult to detect in paediatric STRA, highlighting the need for paediatric studies.(9) Biomarkers for the sub-group most likely to respond need to be identified in childhood studies. Furthermore, in the context of a maturing immune system, and knowing the regulatory function of eosinophils in immune homeostasis(10), their circulatory depletion in children could be deleterious.

We are concerned that, having achieved approval for a paediatric licence by extrapolation of adult data for one biologic, the pharmaceutical industry will adopt the same approach for the many other biologics currently being approved for adult severe asthma(11). Worryingly, benralizumab, which targets the IL-5 receptor on eosinophils and basophils and results in complete depletion of circulating eosinophils(12-14) has been approved by the US Food and Drug Administration for children >12 years despite only 4% of all participants in the five Phase 3 studies currently published being aged 12-17 years(15). We accept trials are ongoing in adolescents and studies in children are challenging. We also acknowledge regulatory agencies may have provided paediatric approval to avoid children being denied access to novel drugs while evidence is collated. But, surely robust efficacy and safety data are mandatory before a paediatric licence is granted for drugs whose potential harmful effects cannot be predicted from adult studies. If licences are granted then post-marketing surveillance must be mandated. Without steps like these, biologics for children will creep into GINA and other guidelines without any evidence base.

To address the current age-discrimination against children in the UK, we have united as a paediatric respiratory community to undertake a clinical trial funded by the National Institute for Health Research (NIHR). We will use a unified clinical protocol including at least 8 weeks electronic adherence monitoring prior to randomisation. The **“Treating severe paediatric asthma; a randomised trial of mepolizumab and omalizumab (TREAT) trial”** will compare the efficacy of omalizumab and mepolizumab in children with STRA. It is a non-inferiority trial over 52 weeks with asthma attacks as the primary outcome, also investigating biomarkers for response in children. As with the adult PREDICTUMAB trial(16) endorsed by the European Respiratory Society, TREAT is a pragmatic trial to determine which biologic is best for which individual child. Importantly, we will aim to demonstrate the advantages of specialist paediatric centres and encourage childhood STRA to also be commissioned as a specialist service. This framework should also be attractive for the pharmaceutical industry to engage with paediatricians to design future trials specifically for children and enable efficient recruitment and regulatory approval. The need for pragmatic trials will increase exponentially and we are grateful to the NIHR for having the foresight to fund TREAT. UK children with severe asthma cannot continue to be treated as second class citizens.

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